A COMPARATIVE STUDY OF EFFICACY AND SAFETY BETWEEN TOPIRAMATE, DISODIUM VALPROATE AND FLUNARIZINE IN MIGRAINE PROPHYLAXIS WITH EPISODIC HEADACHE.

Kundu Avijit [1*], Dutta Arup Kumar [2], SahaRoy Sukalyan [1], Ghosh Abhishek [1]

[1] Resident, Department of Pharmacology, R G Kar Medical College, Kolkata 4.

[2] Assistant Professor, Department of Neurology, R G Kar Medical College, Kolkata 4.

Corresponding author's Email – 1121983avijitk@gmail.com Mob: 08961247473

ABSTRACT:

Migraine headache is associated with significant disability and impaired quality of life. Low dose Topiramate and Divalproex have been shown to be effective in migraine prophylaxis. In this study we wanted to see the relative efficacy & tolerability of low dose Topiramate, Divalproex sodium and Flunarizine as monotherapy in prophylaxis of migraine.132 patients were enrolled in this randomized, double blind, unicentric parallel group study and given Topiramate 50mg/day, Sustained release Divalproex sodium 500 mg/day, Flunarizine 10 mg/day respectively in the three treatment arm. Patients were followed up after every 2 week. At every visit MIDAS Questionnaire, Intensity, Frequency, Duration, Number of episodes requiring Rescue medications were noted.The decrement in frequency of attacks in Topiramate arm was noted to be significantly lower than the other two groups. earliest responders were found in Divalproex treatment arm. 50% reduction in headache frequency occurred by 6th week in Divalproex treatment arm where as in other two treatment arms decreased by 8th week. In all the treatment arms there has been significant decrement in headache intensity, duration of attack, MIDAS score without any significant intergroup difference.Divalproex is quicker than Flunarizine in decreasing headache frequency by 50%. Divalproate's observed benefit may ultimately result from a combination of actions at different loci in brain. Low dose Topiramate is effective as prophylactic but inferior to standard dose of Divalproex. Other than headache frequency there has been no significant difference among the three drugs in other parameters.

Key words: *migraine prophylaxis, frequency, MIDAS, Divalproex, Topiramate, VAS.*

INTRODUCTION:

Migraine headache is second most common cause of headache (1) characterized by severe, pulsatile, mostly unilateral headaches accompanied by vomiting, nausea and autonomic dysfunctions (2). It is associated with significant disability and impaired quality of life (3) and adversely affecting daily activity and work-related productivity for many persons (4). Approximately 15% of the women and 6% men over one year period experience migraine (1). Many migraine patients do not consult a physician for treatment, and even among patients who are treated, less than one third report consistently effective results with their current pharmacologic regimens, most of which include over-the-counter analgesics (5). Furthermore, most migraine patients require bed rest in addition to medication, indicating that migraine continues to significantly affect their lives (5).

The goals of managing migraine are to reduce migraine frequency, severity, and disability; reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies; improve quality of life; reduce headache-related distress and psychologic symptoms; educate patients and enable them to manage their disease; and avoid dose escalation of acute medications (6).

Recent studies suggest that habitual overuse of acute medications, including triptans, ergots, and other analgesics, can lead to the development of chronic daily headaches (7). So preventive medications can serve an important role in the treatment of migraine by reducing migraine frequency and by ameliorating dose escalation and the potential for overuse of acute pharmacotherapies (8).

FDA approved drugs that have the capacity to stabilize the migraine include Propranolol, Timolol, SodiumValproate ,Topiramate and Methysergide.Other than these a number of other drugs appear to display efficacy are Amitryptiline, Flunarizine, Gabapentin, Cyproheptadine(1).

Usually there is a lag period of atleast 2-12 weeks before an effect is seen. According to AHS/AAN guideline 2012 Topiramate (25-200mg/day), Divalproate Sodium(400-1000mg/day) has been rated as level A evidence(should be offered to patients requiring migraine prophylaxis for episodic headche) (9)

Despite all showing good action against migraine recurrence, the aim of our study was whether different mechanism of action of Flunarizine and anticonvulsants (topiramate, valproate) can result in any difference in their effects.

In this proposed study we wanted to see the relative efficacy and tolerability of Low dose Topiramate, Disodium Valproate and Flunarizine as monotherapy in prophylaxis of migraine.

MATERIALS AND METHODS

Objective:

The aim of the study is to compare the efficacy, tolerability, duration of onset of action as prophylactic monotherapy between Topiramate, Disodium valproate and Flunarizine.

Primary objective:

Change in mean fortnight Migraine frequency from baseline in the three treatment arms i.e. Topiramate, Disodium Valproate and Flunarizine.

Secondary objective:

1. Responder rates (Proportion of patients with ≥ 50% reduction in monthly migraine frequency) in the three treatment arms and to see the earliest responder rate among the three treatment arms.

2. Change in MIDAS (Migraine Disability Assessment Score) from baseline and after receiving treatment for three months.

3. Change in Headache Intensity analyzed by VAS (visual analogue scale) from baseline at every fortnight throughout the period of three months.

4. Change in headache duration from baseline at the end of three months in the three treatment modalities.

5. Change in the number of episodes requiring emergency medicines to terminate acute attack from baseline after every 2wk throughout the period of three months.

Ethical considerations:

Study was conducted with full approval from Institutional Ethics Committee. Each patient signed an informed consent form which confirmed the current revision of the declaration of Helsinki.

Design: Randomized, double blind, Unicentric parallel group study.

Inclusion Criteria:

1. Patients having established history of migraine with or without aura as assessed by International Headache Society criteria for at least 6 months. (Appendix 1)

2. Age between 12-60 years.

3. Patients experiencing between 5-14 migraine headaches but not more than 15 headache days per month during prospective baseline visit.(A headache was defined as a calendar day during which patient experienced headache for at least 30 minutes.)

4.. Female of child bearing potential could participate provided they had negative pregnancy test and practicing barrier method of birth control during the two month study period.

Exclusion criteria:

1. Patients were excluded from the study if they experienced headaches other than migraine like Episodic Tension headche, Cluster Headche, Paroxysmal Hemicrania, Chronic Daily Headache or sinus headaches. Although episodic tension and sinus headaches were not expected to respond to treatment, the data were tabulated to confirm that these allowable headaches were accurately captured and excluded.

2. Patients with past history of blunt trauma, Meningitis , Encephalitis, Hypertension, Ischemic heart disease were not included.

3. Previously on migraine prophylaxis within last 2 months.

4. Headaches due to suspected medication overuse if they overused analgesics or specific agents for the acute treatment of migraine episodes. Examples of analgesic overuse included the following: more than 10 treatment episodes/month (episode defined as any calendar day of usage) of ergot-containing medications, Triptans, Opioids (ICHD-II Criteria); more than 15 treatment episodes of Simple Analgesics per month on a regular basis for >3 months.

Patients were excluded if they are on continued use of following medications for any medical reasons like: beta blockers, Tricyclic Anti Depressants, Anti Epileptics, Calcium Channel Blockers ,NSAIDs daily, Botulinum Toxin etc.

5. Patients with history of Nephrolithiasis, Hepatic Ailment, Depression, Parkinsonism were not included in study population.

METHODOLOGY:

132 patients were enrolled in the study as per inclusion and exclusion criteria at screening visit at Neuromedicine OPD and they were assigned to one of the three treatment groups according to a computer generated randomization schedule.

Patient received Topiramate 50mg/day, Sustained release Disodium Valproate 500 mg/day, Flunarizine 10 mg/day respectively in the three treatment arm. Drugs were supplied from the Neurology OPD.

At baseline (screening visit), patients enrolled in the three groups completed MIDAS questionnaire. Patients were followed up after every 2 week. At every visit MIDAS Questionnaire, Intensity, Frequency, Duration, Number of episodes requiring Rescue medications were noted. Patients were asked to maintain a Headache Diary where the frequency, duration and number of episodes requiring SOS medications were noted.

Any adverse event if noticed during the study period were brought to the notice of Consulting physician and also the adverse event reported to the Adverse Drug Reaction Monitoring Centre at R.G.Kar Medical College. The Date of starting, Date of Recovery, Date of Reporting, Intensity, Activities taken on Drug Regime and subject Outcome were noted meticulously. Patients were warned about Topiramate's established adverse effects like Paresthesia, Cognitive symptoms, weight loss, Glaucoma, Nephrolithiasis. Hence in every monthly visit the patients were routinely examined in Opthalmology OPD for Intraoccular Tension, USG of kidney Ureter Bladder to rule out nephrolithiasis.

Likewise treatment arm receiving Valproate were warned about hematologic and liver abnormalities and hence forth underwent complete hemogram and liver function test in all follow up visits. Menstrual history was noted in each visit because of teratogenic potential of Valproate.

In case of Flunarizine patients were carefully examined to rule out any development of signs of Parkinsonism like tremor, bradykinesia etc. In case of any development adverse events due to the drug, the drugs were discontinued, and necessary treatments were given and patients were not enrolled in the study.

Statistical analysis:

For assessment of difference in change in Frequency of headache, Intensity of headache (VAS scores), requirement of episodes of SOS medicines at every fortnight between the treatment arms Kruskal-Wallis test (non-parametric ANOVA) was applied, and for changes within each of treatment arms, Friedman's Test (non-parametric repeated measure ANOVA) was applied followed by Dunn's multiple comparison test.

Reduction in Duration of single episode of headache and MIDAS score from baseline to 12wk individually in each treatment arms was assessed by Paired t Test and change in these two parameters among the treatment arms was assessed by Kruskal Wallis test. Intention to treat Analysis was applied in each treatment arms for analysis of results of all parameters.

RESULT:

Out of 132 patients recruited, 95 were female (71.97 %). Most of them were in 3rd decade of age. 2 patients in Divalproate group needed to discontinue because of significantly raised SGPT level (more than 3 fold compared to

baseline value). 2 patients in Topiramate group intended to change medication due to dyspepsia and nausea. 2 patients in Topiramate group reported paraesthesia.

Table No 1: Demographic parameters

Demographic Parameters	Treatment groups			Significant difference
	Flunarizine	Topiramate	Divalproex	
no of subjects recruited	44	44	44	ns
female (% of total)	34 (77.27 %)	32 (72.72 %)	29 (65.90 %)	ns
male (% of total)	10	12	15	ns
Average age (mean ± SEM) in yrs	30.74 ± 1.626	31.42 ± 1.433	29.21 ± 1.548	0.197/ ns
subjects completed the trial	41	39	40	ns

Efficacy parameters:

Frequency:

Mean fortnightly frequency of migraine attacks have decreased significantly by all 3 medications earliest by 6 weeks.(Table 3) of initiation of treatment. But (during 4^{th} , 5^{th}, 6^{th} and 7^{th} visit) decrement of frequency of attacks in Topiramate treatment arm in comparison to Divalproate and Flunarizine was noted to be significantly lower than the other groups.(Table:2)**.** Among all the three treatment arms earliest reduction in Headache frequency has been observed in Divalproate group by 6wks whereas in the other two treatments this was achieved by 8wks.

Table 2: difference of fortnightly frequency of Migraine between the treatment groups.

	Frequency of Headache (fortnightly) Mean ± SD			Difference between groups		
No of Visits	Flunarizine (Gr **A**)	Topiramate (Gr **B**)	Divalproex (Gr **C**)	**P AB**	**P BC**	**P CA**
Baseline	4.8 ± 1.315	4.7± 1.333	4.75± 1.369	N O T S I G N I FI C A N T		
2nd week	3.95 ± 1.29	4.09± 1.269	4.09 ± 1.192	N O T S I G N I FI C A N T		
4th week	3.18 ± 0.853	3.27 ± 1.163	2.59 ± 0.666*	> 0.05	> 0.05	> 0.05
6th week	2.55 ± 0.671*	2.68 ± 0.716*	2.18 ± 0.395*	> 0.05	**< 0.05**	> 0.05
8th week	1.64 ± 0.492*	1.9 ± 0.526*	1.45 ± 0.509*	> 0.05	**< 0.05**	> 0.05
10th week	0.91 ± 0.294*	1.18 ± 0.395*	0.82 ± 0.588*	> 0.05	**< 0.05**	> 0.05
12th week	0.5 ± 0.512*	0.86± 0.726*	0.27 ± 0.631*	> 0.05	**< 0.05**	> 0.05

*significant Difference compared to baseline, $p < 0.05$,

Table 3: difference of average Frequency of headache per fortnight within each treatment group, expressed as Mean ± SD

D I F F E R E N C E W I T H I N E A C H G R O U P (FREQUENCY)							
	Baseline (a)	**2nd Week (b)**	**4th Week (c)**	**6th Week (d)**	**8th Week (e)**	**10th Week (f)**	**12th Week (g)**
Flunarizine	4.8 ± 1.315	3.95 ± 1.29	3.18 ± 0.853	2.55 ± 0.671	1.64 ± 0.492	0.91 ± 0.294	0.5 ± 0.512
		P ab > 0.05	P bc > 0.05 P ac > 0.05	P cd > 0.05 P bd > 0.05 **P ad < 0.01**	P de > 0.05 **P ce < 0.05**	P ef > 0.05 **P df < 0.001** **P df < 0.01**	P fg > 0.05 P eg > 0.05 **P dg < 0.001**
Topiramate	4.7 ± 1.333	4.09 ± 1.269	3.27 ± 1.163	2.68 ± 0.716	1.9 ± 0.526	1.18 ± 0.395	0.86± 0.726
		P ab > 0.05	P bc > 0.05 P ac > 0.05	P cd > 0.05 P bd > 0.05 P ad < **0.01**	P de > 0.05 P ce > 0.05 **P be < 0.001** **P ae <0.001**	P ef > 0.05 P df < 0**.05**	P fg > 0.05 P eg > 0.05 **P dg < 0.001**
Divalproex	4.75 ± 1.369	4.09 ± 1.192	2.59 ± 0.666	**2.18** ± 0.395 (> 50% reduction)	1.45 ± 0.509	0.82 ± 0.588	0.27 ± 0.631
		P ab > 0.05	P bc > 0.05 **P ac < 0.05**	P ad **< 0.001** P cd > 0.05 **P bd >** 0.05	P de > 0.05 P ce > 0.05 **P be < 0.001**	P ef > 0.05 **P df < 0.05**	P fg > 0.05 P eg > 0.05 **P dg < 0.001**

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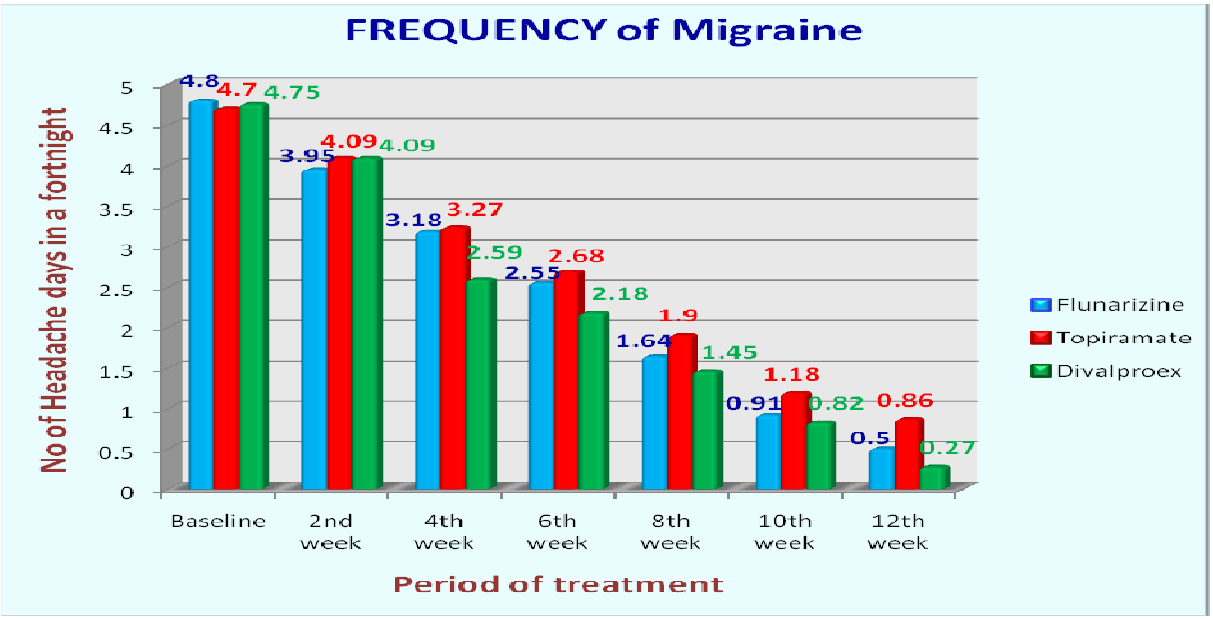

Figure - 1: Column diagram showing Frequency of Migraine attacks per fortnight in each treatment group.

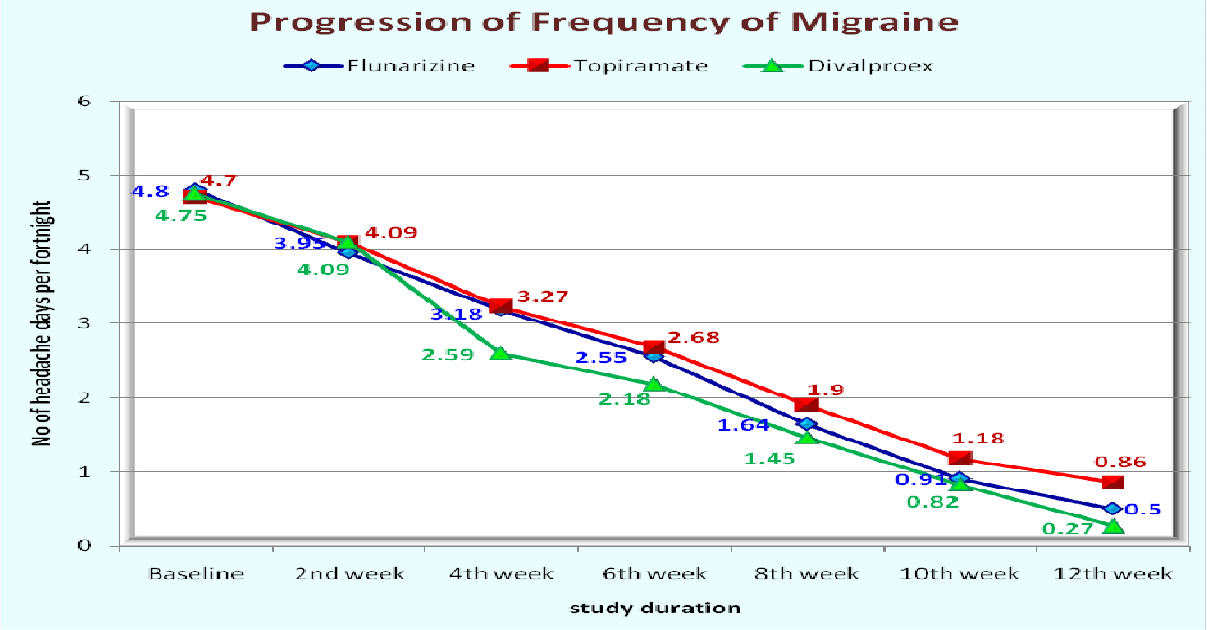

Figure - 2: Line diagram showing progress of fortnightly frequency of Migraine attacks with treatment in different groups.

(2) Intensity of migraine headache: Mean fortnightly VAS score of migraine attacks have been analyzed in all 3 treatment arms. In each treatment arm the change was significant after 6week of initiation of treatment. Applying Friedman's test with Dunn's post hoc analysis revealed within each treatment arm the difference in VAS score was significant after every 4 week. (Table 4).

- There has been no significant difference among the three treatment arms in reduction of VAS score. (Table 5)

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Table - 4: difference of average VAS scores per fortnight within each treatment group, expressed as Mean ± SD.

DIFFERENCE WITHIN EACH GROUP (INTENSITY)							
	Baseline (a)	**2nd Week (b)**	**4th Week (c)**	**6th Week (d)**	**8th Week (e)**	**10th Week (f)**	**12th Week (g)**
Flunarizine	**7.54 ± 0.876**	**6.86 ± 0.965**	**5.55 ± 0.964**	**3.94 ± 0.852**	**2.77 ± 0.667**	**1.49 ± 0.903**	**0.7 ± 0.816**
		P ab > 0.05	P bc > 0.05 P ac > 0.05	P cd >0.05 **P bd<0.05** **Pad<0.001**	P de > 0.05 **P ce <0.05** **P ae<0.001**	P ef > 0.05 **P df < 0.05**	P fg > 0.05 P eg > 0.05 **Pdg<0.001**
Topiramate	**7.63 ± 0.951**	**6.93 ± 0.96**	**5.77 ± 0.873**	**3.75 ± 0.813**	**2.61 ± 0.554**	**1.64 ± 0.996**	**1.03 ± 1.179**
		P ab > 0.05	P bc > 0.05 P ac > 0.05	P cd >0.05 P bd< 0.05 Pad<0.001	P de >0.05 **P ce <0.05**	P ef > 0.05 **P df < 0.05**	P fg > 0.05 P eg > 0.05 **P dg < 0.01**
Divalproex	**7.74 ± 0.886**	**6.89 ± 0.929**	**5.5 ± 0.921**	**3.69 ± 0.81**	**2.51 ± 0.526**	**1.47 ± 1.011**	**0.85 ± 1.106**
		P ab > 0.05	P bc > 0.05 **P ac < 0.05**	P cd >0.05 **P bd<0.05** **Pad<0.001**	P de > 0.05 **P ce < 0.05**	P ef > 0.05 **P df < 0.05**	P fg > 0.05 P eg > 0.05 **P dg < 0.01**

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Table - 5: difference of average VAS scores between the treatment groups.

	INTENSITY of Headache (fortnightly) **Average** VAS score (Mean ± SD)			Difference between groups		
No of Visits	**Flunarizine (Gr A)**	**Topiramate (Gr B)**	**Divalproex (Gr C)**	**P AB**	**P BC**	**P CA**
Baseline	7.54 ± 0.876	7.63 ± 0.951	7.74 ± 0.886	Not significant		
2nd week	6.86 ± 0.965	6.93 ± 0.96	6.89 ± 0.929	Not significant		
4th week	5.55 ± 0.964	5.77± 0.873	5.5 ± 0.921	Not significant		
6th week	3.94 ± 0.852	3.75 ± 0.813	3.69 ± 0.81	Not significant		
8th week	2.77 ± 0.667	2.61 ± 0.554	2.51 ± 0.526	Not significant		
10th week	1.49 ± 0.903	1.64 ± 0.996	1.47 ± 1.011	Not significant		
12th week	0.7 ± 0.816	1.03 ± 1.179	0.85 ± 1.106	Not significant		

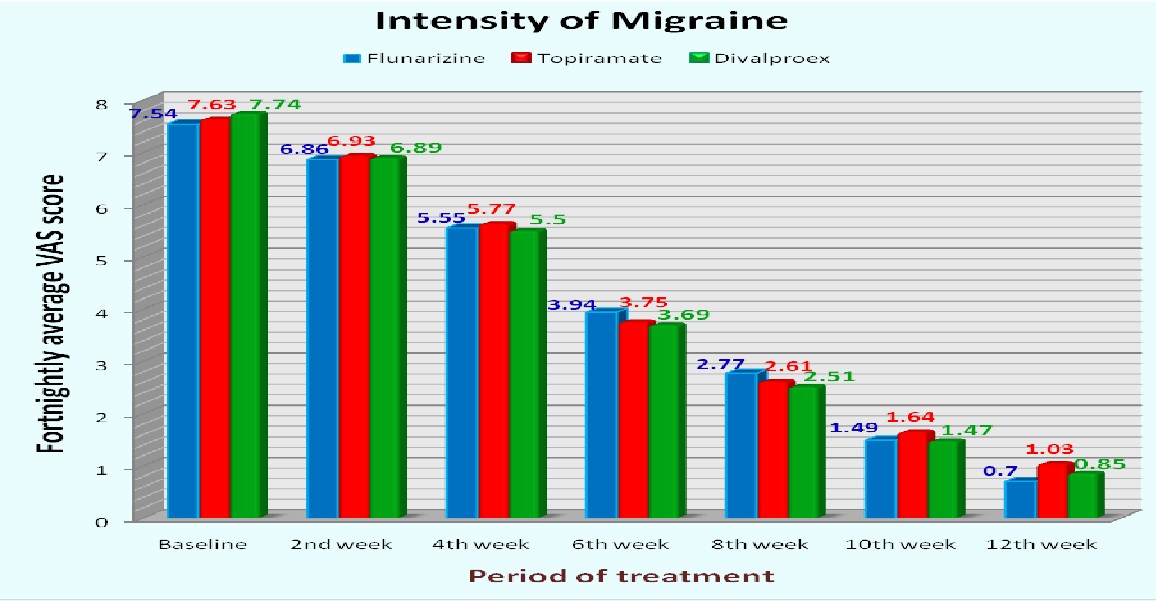

Figure 3: Column diagram showing intensity of Migraine attacks determined by average VAS SCORE per fortnight in different treatment groups.

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(3) **Duration of single migraine attack**: Duration of longest single headache episode has decreased significantly by all 3 medications as compared to baseline (1st visit) value, as noted at the end of trial. (Table:6) (Figure:4)

Table 6: **showing difference of duration of longest episode of headache between the treatment groups**.

	Duration in Hour **m e a n ± S E M**			
No of Visit	Flunarizine	Topiramate	Divalproex	significant difference **(Kruskal-Wallis)**
1st Visit	11.55 ± 1.019	10.91 ± 1.26	11.32 ± 1.347	Not Significant
7th Visit	1.59 ± 0.157	1.11 ± 0.122	1.34 ± 0.162	Not Significant
P (paired-t)	< 0.0001	< 0.0001	< 0.0001	

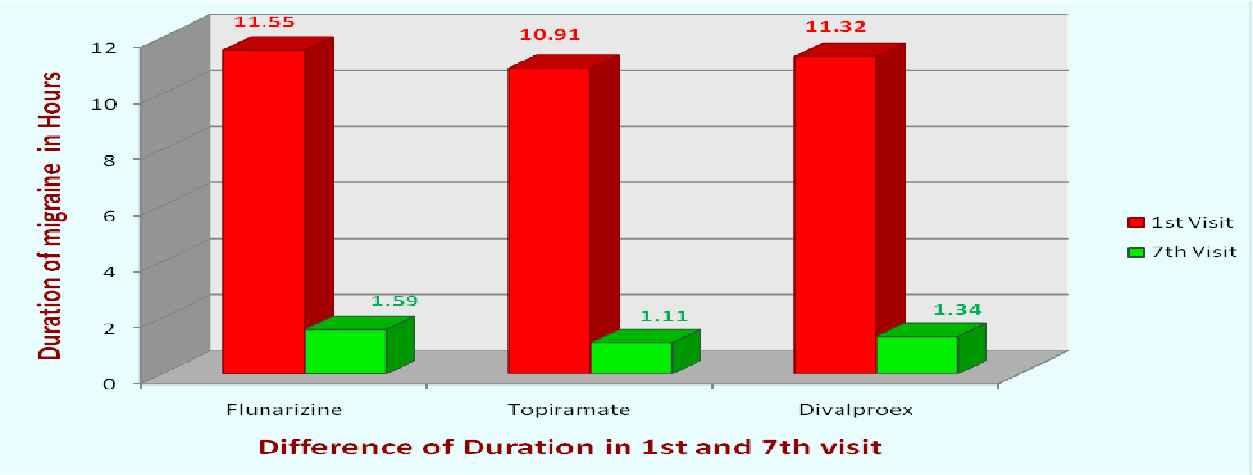

Figure 4: **Diagram showing duration of Migraine in Hours in 1st and last visit in different treatment groups**.

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(4) **MIDAS score**: 3 month MIDAS scores have significantly decreased in all groups as noted at the end of the trial, compared to baseline (1st visit) value.
(Table: 7 and Figure:5)

Table no 7: showing difference of MIDAS score among the treatment groups.

	MIDAS (M e a n ± S E M)			
No of Visit	Flunarizine	Topiramate	Divalproex	significant difference
1st Visit	33.82 ± 1.783	34.05 ± 1.632	32.68 ± 1.624	not significant
7th Visit	4.55 ± 0.533	3.73 ± 0.543	3.32 ± 0.507	not significant
P	< 0.0001	< 0.0001	< 0.0001	

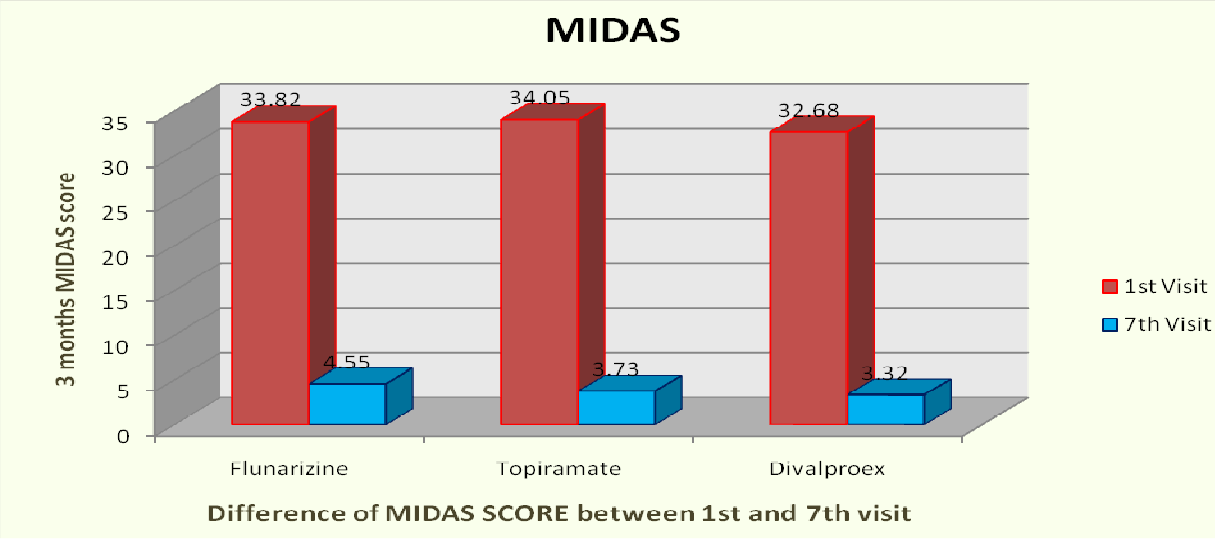

Figure 5: Column diagram showing MIDAS scores (mean ± SEM) of different treatment groups in 1st and last visit.

(5) Requirement of SOS medications : Need for SOS medications (as expressed by number of tablets consumed in a fortnight to terminate the acute attack of headche) decreased significantly after 6weeks(4th visit) of initiation of therapy, as compared to baseline (1st visit/0 week) value. There is no significant difference among the three treatment groups.(Table:8 and Figure:6)

Table 8 : showing difference of SOS medication among the treatment groups.

	No of SOS medication mean ± S E M			difference between groups		
no of Visit	Flunarizine (Group **A**)	Topiramate (Group **B**)	Divalproex (Group **C**)	**$_P$AB**	**$_P$ BC**	**$_P$ CA**
1 (baseline)	5.23	4.95	5.18	Not significant		
2	4.73	4.36	4.73	N o t significant		
3	3.81	3.56	3.64	N o t significant		
4	2.66*	2.49*	2.51*	N o t significant		
5	1.57*	1.68*	1.32*	N o t significant		
6	1.09*	1.16*	0.91*	N o t significant		
7	0.45*	0.59*	0.41*	N o t significant		
' * ' - significant change compared to baseline						

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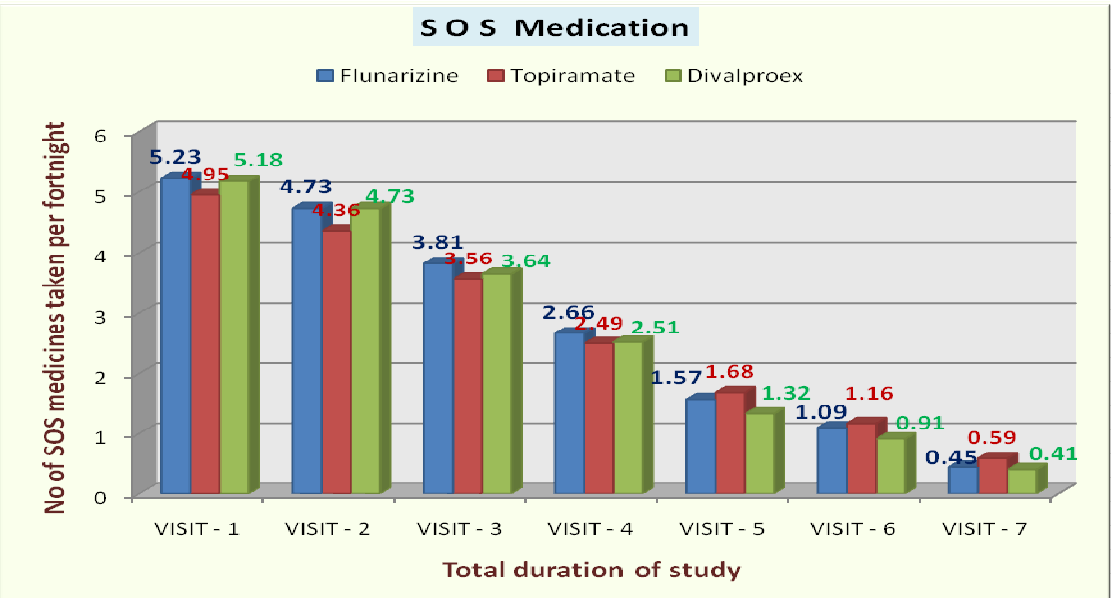

Figure 6: Column diagram showing numbers of SOS medication consumed per fortnight in different treatment groups.

DISCUSSION:

Topiramate has multiple mechanisms of action that could contribute to migraine prevention, including state-dependent inhibition of voltage-gated sodium channels, inhibition of high-voltage–activated calcium channels, inhibition of glutamate-mediated neurotransmission at α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate receptor subtypes, and enhancement of γ-aminobutyric-acid$_A$-receptor–mediated chloride flux (10). Recent research suggests that topiramate may also modulate trigeminovascular signaling, which could affect migraine pathogenesis (11).

Valproate has been shown to be an effective prophylactic treatment in migraine. Investigation of the mechanism of its antimigraine action is difficult due to the broad range of its biochemical effects and the complex nature of migraine pathophysiology. Valproate increases brain GABA levels and, in doing so, may suppress migraine-related events in the cortex, perivascular parasympathetics or trigeminal nucleus caudalis. There is experimental evidence that it suppresses neurogenic inflammation and directly attenuates nociceptive neurotransmission. In addition, valproate reportedly alters levels of excitatory and inhibitory neurotransmitters and exerts direct effects on neuronal membranes in vitro. Valproate's observed effect may ultimately result from a combination of actions at different loci (12).

Flunarizine is being used as a first line agent in migraine prophylaxis in our Neurology OPD.

The main mechanism of Flunarizine in prevention of recurrent migraine is most likely to be the neurogenic effect in influencing the release of neurotransmitter such as dopamine and met-enkephalin and by blocking calcium and sodium channels (13, 14). It is less likely to be the vascular effect according to the failure of transcranial doppler sonography to demonstrate significant change in blood flow velocity measured in the middle cerebral artery and basal artery after treatment with intravenous Flunarizine during a migraine attack (15).

In our study there was significant difference in decrement of frequency of attacks in Topiramate treatment arm in comparison to Divalproate and Flunarizine from 6th week onwards up to 12weeks (end of study). The decrement in frequency of attacks in Topiramate arm was noted to be significantly lower than the other two groups. So in this respect low dose Topiramate was inferior to Divalproate and Flunarizine though the change in frequency of headache attacks significantly decreased in all the three treatment arms earliest by 6weeks. Unlike earlier studies in episodic migraine prophylaxis, Topiramate is inferior to Divalproate and Flunarizine in reducing migraine headache frequency.

Moreover earliest responders were found in Divalproate treatment arm. 50% reduction in headache frequency occurred by 6th week in Divalproate treatment arm where as in other two treatment arms decreased by 8th week.

So overall considering all the aspects Divalproate turns out to be better in comparison to Topiramate and Flunarizine in providing relief in Headache frequency providing earliest relief in decreasing headache frequency. The reason behind this quick benefit of Divalproate in comparison to other two drugs in this head to head trial is difficult to ascertain directly due to the broad range of Divalproate's biochemical effects and the complex nature of migraine pathophysiology. Divalproate increases brain GABA levels and, in doing so, may suppress migraine-related events in the cortex, perivascular parasympathetics or trigeminal nucleus caudalis. There is experimental evidence of Divalproate suppressing neurogenic inflammation and directly attenuating nociceptive neurotransmission. In addition, Divalproate reportedly alters levels of excitatory and inhibitory neurotransmitters and exerts direct effects on neuronal membranes in vitro. Divalproate's observed benefit may ultimately result from a combination of actions at different loci in brain.

In all the treatment arms there has been significant decrement in headache intensity earliest by 6th week. But there has been no significant difference between the three treatment arms in decrement of headache intensity.

Duration of single migraine headache episode have decreased in all the treatment arms significantly after 3months of treatment but there has been no significant difference among the three treatment modalities.

Like earlier trials in all the treatment arms there has been significant decrement in MIDAS score at the end of three arms without any intergroup difference suggestive of equal effectiveness in improvement in quality of life. So Divalproate, Topiramate, Flunarizine were equally effective in terms of improving the quality of life in Migraine patients.

The number of requirement of SOS medications in every fortnight in all the treatment groups decreased significantly at the end of 4weekscompared to the baseline 1st visit.

CONCLUSION:

We can conclude that in this head to head trial among three anti migraine drugs as prophylaxis in contrast to earlier studies in this eastern part of India, Divalproate is quicker than Flunarizine in decreasing headache frequency by 50%. Topiramate stands out to be inferior in comparison to Divalproate and Flunarizne. Other than headache frequency there has been no significant difference among the three drugs in other parameters of Migraine headache like reducing intensity of headache(assessed by MIDAS score), improvement in Quality of life (assessed by MIDAS score), reduction in requirement of SOS medicines to terminate acute headache.

REFERENCES:

1.Goadsby Peter J,Raskin Neil H,Headche ,D.L.long et al(eds) Harrison's Principles of Internal Medicine, Part 2,vol-1,18th ed, New York:Mc Graw-Hill,2011,14:114-117

2. R. Bavrasad, S.E.M. Nejad, A.R. Yarahmadi, S.I. Sajedi and F. Rahim, 2010. Assessment of the Middle Dose of Topiramate in Comparison with Sodium Valproate for Migraine Prophylaxis: A Randomized-Double-Blind Study. *International Journal of Pharmacology, 6: 670-675.*

3. Lipton RB, Hamelsky SW, Kolodner KB, Steiner TJ, Stewart WF. Migraine, quality of life, and depression: a population-based case-control study. *Neurology.*2000;55:629-635.

4. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States: disability and economic costs. *Arch Intern Med.*1999;159:813-818

5. Brandes JL. Global trends in migraine care: results from the MAZE survey. *CNS Drugs.*2002;16(suppl 1):13-18.

6. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.*2000;55:754-762.

7. Limmroth V, Katsarava Z, Fritsche G, Przywara S, Diener HC. Features of medication overuse headache following overuse of different acute headache drugs. *Neurology.*2002;59:1011-1014.

8. Jan Lewis Brandes, MD; Joel R. Saper, MD; Merle Diamond, MD; James R. Couch, MD, PhD; Donald W. Lewis, MD; Jennifer Schmitt, MS; Walter Neto, MD; Stefan Schwabe, MD; David Jacobs, MD; for the MIGR-002 Study Group *JAMA*. 2004;291(8):965-973. doi:10.1001/jama.291.8.965

9. AHS/AAN Guideline

10. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. *Epilepsia.*2000;41(suppl 1):S3-S9.

11. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. *Epilepsia.*2000;41(suppl 1):S3-S9.\

12. Cutrer FM, Limmroth V, Moskowitz MA, Possible mechanisms of valproate in migraine prophylaxis, Cephalalgia. 1997 Apr;17(2):93-100.

13. Cutrer FM, Limmroth V, Moskowitz MA, Possible mechanisms of valproate in migraine prophylaxis, Cephalalgia. 1997 Apr;17(2):93-100

14. Lauritzen M. Cortical spreading depression in migraine. Cephalalgia 2001; 21:757-60.

15. . Diener HC, Matias-Guiu J, Hartung E, et al. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160mg daily. Cephalalgia 2002; 22: 209-21